REMARKS

Reconsideration of this application is respectfully requested.

Claims 68-72 are new and are fully supported by the specification, as discussed below. Upon amendment, claims 65-72 are pending in this application.

Claims 65-67 were rejected under 35 U.S.C. § 112, first paragraph, for allegedly containing subject matter that was not described in the specification in such way as to reasonably convey that applicants had possession of the claimed invention at the time the application was filed. The Examiner contends that nothing in the specification would lead the skilled artisan to the currently claimed species.

Applicants traverse the rejection. As previously set forth in applicants' February 19, 2004, Amendment, November 12, 2003, Supplemental Amendment, and August 25, 2003, Amendment, and as further discussed below, applicants' specification adequately supports the claimed invention.

The specification describes variants of HIV-1ELI

Applicants isolated a novel HIV-1 isolate, HIV-1ELI, and provided its complete nucleotide sequence. (Specification at Fig. 7.) The specification indicates that the invention includes "variants" of HIV-1ELI having a nucleotide sequence different from that of HIV-1ELI due to deletions and mutations:

> In accordance with this invention, a new virus has been discovered that is responsible for diseases clinically related to AIDS and that can be classified as a LAV-1 virus but that differs genetically from known LAV-1 viruses to a much larger extent than the known LAV-1 viruses differ from each other. The new virus is basically characterized by the cDNA sequence which is shown in Figures 7A to 7I, and **this new virus is hereinafter generally referred to as "LAV_{ELI}"**.
>
> Also in accordance with this invention, **variants of the new virus are provided**. The RNAs of these variants and the related cDNAs derived from said RNAs are hybridizable to corresponding parts of the

> cDNA of LAV_{ELI}. The DNA of the new virus also is provided, as well as DNA fragments derived therefrom hybridizable with the genomic RNA of LAV_{ELI}, such DNA and DNA fragments particularly consisting of the cDNA or cDNA fragments of LAV_{ELI} or of recombinant DNAs containing such cDNA or cDNA fragments.
>
> DNA recombinants containing the DNA or DNA fragments of LAV_{ELI} or its variants are also provided. It is of course understood that fragments which **would include some deletions or mutations** which would not substantially alter their capability of also hybridizing with the retroviral genome of LAV_{ELI} are to be considered as forming obvious equivalents of the DNA or DNA fragments referred to hereinabove.

(*Id.* at 3; emphasis added.)

The specification also discloses an HIV-1ELI variant, HIV-1MAL, and provides the nucleotide sequence of its Env protein. (*Id.* at Fig. 3.) The specification leaves no doubt that applicants contemplated that variants of HIV-1ELI were part of the invention:

> Needless to say, **the invention extends to all variants of genomes and corresponding DNA fragments (ORFs) having substantially equivalent properties, all of said genomes belonging to retroviruses which can be considered as equivalents of LAV_{ELI}.** It must be understood that the claims which follow are also intended to cover all equivalents of the products (glycoproteins, polypeptides, DNAs, etc.) whereby an equivalent is a product, e.g., a polypeptide, which may distinguish from a product defined in any of said claims, say through one or several amino acids, while still having substantially the same immunological or immunogenic properties. A similar rule of equivalency shall apply to the DNAs, it being understood that the rule of equivalency will then be tied to the rule of equivalency pertaining to the polypeptides which they encode.

(*Id.* at 35; emphasis added.)

The specification directs the skilled artisan to the claimed HIV-1ELI variants

Applicants' specification, when read "as a whole," leads the skilled artisan to the claimed HIV-1ELI variants. Applicants compared the nucleotide and amino acid sequences of HIV-1ELI with three known HIV-1 viruses, HIV-1IIIB, HIV-1BRU, and

HIV-1ARV-2. (*Id.* at 2, lines 2-6.) The nucleotide sequence of HIV-1ELI differed from the known HIV-1 viruses to a much greater extent than the sequences of the known viruses differed from each other. (*Id.* at 2, lines 30-35.) Thus, applicants discovered that the heterogeneity of HIV-1 was much greater than that which had been previously appreciated. Applicants' claims recite a virus encoding an Env protein that comprises amino acids of HIV-1ELI Env protein that are not present in the three known viruses.

The specification describes the existence of conserved domains in the envelope region of the genome, with little or no genetic variation:

> From the alignment of figure 3 and the graphical representation of the envelope variability shown in figure, we clearly see **the existence of conserved domains, with little or no genetic variation**, and hypervariable domains, in which even the alignment of the different sequences is very difficult, because of the existence of a large number of mutations and of reciprocal insertions and deletions. We have not included the sequence of the envelope of the HTLV-3 isolate since it is so close to that of LAV_{BRU} (cf. fig. 4), even in the hypervariable domains, that it did not add anything to the analysis. While this graphical representation will be refined by more sequence data, the general profile is already apparent, with three hypervariable domains (Hyl, 2 and 3) all being located in the OMP and separated by **three well-conserved stretches (residues 37-130, 211-289, and 488-530 of fig. 3 alignment)** probably associated with important biological functions.

(*Id.* at 11-12; emphasis added.)

Applicants' specification directs the skilled artisan to proteins containing the conserved regions of HIV1ELI: "[p]roteins containing or consisting of the 'well conserved stretches' are of particular interest . . . ." (*Id.* at 23, lines 21-22.) These "well conserved" stretches included aa 37-130, aa 211-289, aa 488-530, and aa 680-700 of HIV-1ELI Env protein. (*Id.*)

The specification stresses the importance of the conserved regions:

> One or several of the conserved domains of the OMP (residues **37-130, 211-289, and 488-530 of fig. 3** alignment), brought together by the folding of the protein, must play a part in the virus receptor interaction, and this can be explored with synthetic or genetically-engineered peptides derived from these domains, either by direct binding assays or indirectly by assaying the neutralizing activity of specific antibodies raised against them.

(*Id.* at 11-12; emphasis added.) Thus, the specification directs the skilled artisan to viruses containing the "well-conserved" regions of HIV-1 Env in Figure 3. Those amino acid residues that are unique to HIV-1 ELI variants within "well-conserved" regions are illustrated in Figure 3. It is these amino acid residues that are the focus of the pending claims.

As seen in Fig. 3E-1, one of these "well-conserved" stretches, aa 37-130, has the amino acid sequence: LWVTVYYGVPVWKEATTTLFCASDAKSYETEAHNIWAT HACVPTDPNPQEIALENVTENFNMWKNNMVEQMHEDIISLWDQSLKPCVKLTPLCV. These amino acid residues are recited in new claims 68 and 72. This "well-conserved" stretch contains the amino acids S^{63}, E^{65}, A^{68}, I^{71}, I^{87}, A^{88}, and E^{90}, which are present in the sequence of HIV-1ELI and are not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same positions. A variant of HIV-1ELI, HIV-1MAL, contains the amino acids S^{63}, E^{65}, I^{71}, I^{87}, E^{88}, and E^{90}. Thus, the skilled artisan would immediately recognize that the amino acid residues S^{63}, E^{65}, A^{68}, I^{71}, I^{87}, A^{88}, and E^{90} and, especially the amino acid residues S^{63}, E^{65}, I^{71}, I^{87}, and E^{90}, were amino acid residues found in HIV-1ELI variants and not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same positions. These amino acid residues are recited in claims 65-67.

Similarly, Fig. 3E-1 shows that the "well-conserved" stretch at aa 211-289 has the amino acid sequence: CNTSAITQACPKVSFEPIPIHYCAPAGFAILKCRDKKFNGT GPCTNVSTVQCTHGIRPVVSTQLLLNGSLAEEEVIIRS. These amino acid residues are recited in new claims 69 and 72. This "well-conserved" stretch contains the amino acids A^{215}, R^{244}, D^{245}, K^{247}, and I^{286}, which are present in the sequence of HIV-1ELI and are not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same positions. A variant of HIV-1ELI, HIV-1MAL, contains the amino acids D^{245}, K^{247}, and M^{286}. Thus, the skilled artisan would immediately recognize that the amino acid residues A^{215}, R^{244}, D^{245}, K^{247}, and I/M^{286} and, especially the amino acid residues D^{245} and K^{247}, were amino acid residues found in HIV-1ELI variants and not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same positions. These amino acid residues are recited in claims 65-67.

Also, Fig. 3E-2 shows that the "well-conserved" stretch at aa 488-530 has the amino acid sequence: RPGGGDMRDNWRSELYKYKVVQIEPLGVAPTRAKRRVV EREKR. These amino acid residues are recited in new claims 70 and 72. This "well-conserved" stretch contains the amino acids Q^{509}, R^{519}, E^{526}, which are present in the sequence of HIV-1ELI and are not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same positions. A variant of HIV-1ELI, HIV-1MAL, contains the amino acids R^{509} and E^{526}. Thus, the skilled artisan would immediately recognize that the amino acid residues Q/R^{509}, R^{519}, E^{526} and, especially the amino acid residue E^{526}, were amino acid residues found in HIV-1ELI variants and not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same positions. These amino acid residues are recited in claims 65-67.

Lastly, Fig. 3F-1 shows that the "well-conserved" stretch at aa 680-700 has the amino acid sequence: LLELDKWASLWNWFSITQWLW. These amino acid residues are recited in new claim 71. This "well-conserved" stretch contains the amino acid Q^{697}, which is present in the sequence of HIV-1ELI and is not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same position. A variant of HIV-1ELI, HIV-1MAL, contains the amino acid K^{697}. Thus, the skilled artisan would immediately recognize that the amino acid residues K/Q^{697}, were amino acid residues found in HIV-1ELI variants and not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same positions. These amino acid residues are recited in claims 66 and 67.

The specification provides guidance in preparing HIV-1ELI variants.

Applicants' comparisons in Fig. 3 provide a blueprint of amino acids found in HIV-1ELI variants that are not present in the sequences of HIV-1BRU and HIV-1ARV-2 at the same positions. Using this blueprint, the skilled artisan could generate an enormous genus of HIV-1ELI variants containing HIV-1ELI-specific amino acids. For example, the skilled artisan could generate an HIV-1 virus containing any of the HIV-1ELI-specific amino acids sequence variations shown in Fig. 3, such as a serine at aa 63 and/or an isoleucine at aa 71. Moreover, the Examiner has conceded that the specification enables the claimed invention. (Paper No. 15 at 5.) Thus, guidance provided by applicants is sufficient to convey to the skilled artisan that applicants had possession of the claimed invention at the time the application was filed. Accordingly, applicants respectfully request withdrawal of the rejection.

Applicants respectfully submit that this application is in condition for allowance. In the event that the Examiner disagrees, he is invited to call the undersigned to discuss any outstanding issues remaining in this application in order to expedite prosecution.

Please grant any extensions of time required to enter this response and charge any additional required fees to our deposit account 06-0916.

Respectfully submitted,

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